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Routine ultrasonography in utero and subsequent handedness and neurological development

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Abstract

***Objective*—To examine any associations between routine ultrasonography in utero and subsequent brain development as indicated by non-right handedness at primary school age and neurological development during childhood.**

***Design*—Follow up of 8 and 9 year old children of women who took part in two randomised, controlled trials of routine ultrasonography during pregnancy.**

***Setting*—Clinics of 60 general practitioners in Norway during 1979-81. Maternal and child health centres.**

***Subjects*—2161 (89%) of 2428 eligible singletons were followed up, partly through a questionnaire to their parents and partly through information from health centres.**

***Main outcome measures*—The dominant hand of the child was assessed by 10 questions. Deficits in attention, motor control, and perception were evaluated by five questions. Impaired neurological development during the first year of life was assessed by an abbreviated version of the Denver developmental screening test.**

***Results*—The odds of non-right handedness were higher among children who had been screened in utero than among control children (odds ratio 1·32; 95% confidence interval 1·02 to 1·71). No clear differences were found between the groups with regard to deficits in attention, motor control, and perception or neurological development during the first year of life.**

***Conclusion*—Our data suggest a possible association between routine ultrasonography in utero and subsequent non-right handedness, whereas no association with impaired neurological development was found. As the question on non-right handedness was one of six initial hypotheses, the observed results may be due to chance. None the less, the results suggest that the hypothesis may have some merit and should be tested in future studies.**

Introduction

The common indications for diagnostic ultrasound scanning in pregnancy and the routine screening offered in some countries result in most pregnant women in developed countries being exposed to the procedure. No adverse effects of diagnostic ultrasound screening in pregnancy have been reported. Possible long term effects among children exposed to ultrasound in utero, however, have been examined in only a few studies. The general consensus is that further research on this topic is warranted.[1]

Abnormal development is typically related to disturbances during critical stages of gestation. Routine ultrasonography is usually done between the 16th and the 22nd week of pregnancy, which is an important phase of brain development.[2] At this point neurones migrate towards their destination in the fetal brain. Experimental studies in vitro have shown changes in the cell membrane[3] and cell surface motility and architecture[4] after exposure to ultrasound. Ultrasound might influence neuronal migration, and it has been suggested that altered cerebral dominance, dyslexia, or impaired neurological development may be the result of a disturbed migration of neurones.[5] The dominant hand may serve as an indicator of cerebral dominance. The normal high prevalence of right handedness means that random damage to the hemispheres will increase left handedness.[6]

Long term follow up of infants in randomised clinical trials has been recommended to answer questions about the effect of ultrasound on human development.[7] In a previous report we were unable to find any association between routine ultrasonography in utero and poor performance at school or dyslexia among 8 and 9 year old children.[8] Nor did we find any differences in vision or hearing at ages 4 and 7.[9] In the present report on the same children we aimed to find out whether routine ultrasonography was associated with changes in handedness patterns or with impaired neurological development.

Subjects and methods

Two randomised controlled trials of ultrasonographic screening in pregnancy were carried out in the Norwegian cities of Trondheim and Ålesund in 1979-81.[10,11] The study design and methods of randomisation (sealed envelope method) were identical. The pregnant women in Ålesund were representative of the general population,[11] whereas the study population in Trondheim included more low risk pregnancies.[10] The study women were offered ultrasonographic examinations in the 19th and 32nd weeks of pregnancy. The same ultrasonic devices (ADR 2130, Tempe, Arizona) were used in Trondheim and Ålesund. Those scanners produced lower intensities than do most scanners in obstetric use today. The median exposure time for the first routine scan in Ålesund was three minutes.

Altogether 2637 women were randomised into a screening group of 1335 women and 1302 controls. Among the screened women there were 15 pairs of twins, 55 abortions, and eight perinatal deaths among singletons. The whereabouts of 13 women could not be traced eight years after the original studies, leaving 1244 eligible, live born singletons to be followed up in 1988. In the control group, there were 10 pairs of twins, one set of triplets, 66 abortions, 11 perinatal deaths among singletons, three late neonatal deaths, and 27 women who could not be found, leaving 1184 eligible singletons for the present study.

Mothers of all the 2428 eligible children were sent a questionnaire together with an information letter and a postage paid return envelope. The questionnaire consisted of 66 closed questions on sociodemographic data; the child's health, hearing, and vision; and specific questions about dominant hand and neurological development. We specifically included questions about family history of dyslexia, left handedness, and allergy and about social variables such as parental years of education, parental occupation, and family income. Immune diseases were of particular interest because of a reported triadic association among immune disease, dyslexia, and left handedness,[5] and these were covered in four questions. Return of the questionnaire was taken as informed consent for the child to take part in the follow up study. Two reminders were sent to non-responders.

Norwegian children are regularly examined by physicians and specially trained public health nurses at maternal and child health centres. Visits take place when a child is 6 weeks old and at 3, 6, and 12 months and at 2, 4, and 7 years of age. The prospectively recorded data from these examinations were collected for each child in the study. The staff at the maternal and child health centres were not aware of whether the child had been exposed to ultrasound or the objectives of the study.

Among six stated hypotheses in the study protocol, two dealt with vision and hearing and four with possible effects of routine ultrasonography on the developing fetal brain. These included increased incidence of dyslexia; deficits in attention, motor control, and perception; impaired neurological development during the first year of life; and changes in handedness. Analyses of the association between ultrasound scanning and dyslexia have been reported elsewhere.[8]

HANDEDNESS

The dominant hand of the child was assessed with 21 questions taken from a modified version of a questionnaire developed by Rackzowski and coworkers.[12] The parents answered specific questions about which hand the child preferred to use while performing various tasks in daily life activities. They were instructed not to respond if they had never observed the child do the task in question. Response options were the left hand, equally often with either hand, or the right hand.

Before the study we had decided to include questions on a variety of activities and to exclude questions that were not responded to with reasonable frequency. We had not, however, decided which questions to include in the analysis before the study.

Complete data on all 21 questions was available for only 1210 children (50%). In a trade off between increasing statistical power and losing information by dropping questions, we decided to use information from 10 of the 21 questions. These included which hand the child preferred when drawing, writing, dealing cards, using a bottle opener, throwing a ball, using an eraser and a pair of scissors, eating with a spoon and a fork, and cutting with a knife. Complete data were available from 1663 children (69%). The 10 items represented various aspects of activities of the daily life of an 8 or 9 year old child (doing school work, playing games, having a meal, and using a tool) and received a fairly high response rate. A child was classified as being right handed or left handed if at least nine of the 10 questions were answered as such. Children were classified as non-right handed if they were not right handed, thereby including all children who were left handed.

The data were also analysed with a quantitative approach by using a handedness score based on the 10 selected questions. If none of the 10 questions were answered as right handed, the handedness score was 0. If all 10 questions were answered as right handed, the handedness score was 10. The distribution of this laterality score was, of course, highly skewed towards right handedness. Thus, the handedness score was compared between screened and control children with non-parametric statistics.

NEUROLOGICAL DEVELOPMENT DURING FIRST YEAR OF LIFE

Neurological development in infancy is closely monitored at the maternal and child health centres. The original Denver developmental screening test included 105 items which cover four developmental functions in infants and preschool children (gross motor, language, fine motor-adaptive, and personal-social functions).[13] In Norway a modified version with 10 items has been used for the past 20 years, including six items for gross motor functions: prone, lifts the head up 90 degrees (should be achieved by the age of 5 months); rolls over (6 months); sits without support (9 months); pulls self to stand (11 months); walks holding on to furniture (12 months); and walks well (14 months). Four items for personal-social, language, and fine motor-adaptive functions comprise smiles responsively (should be achieved by 4 months); imitates speech sounds (7 months); thumb-finger grasp (10 months); and three words other than "mama" or "dada" (14 months).

A child was included in the analyses if information on at least one of the 10 items from the short version of the Denver test was available. Children were classified as having impaired neurological development if they had not achieved one of the 10 functions at the

expected age. In addition, mothers reported in the questionnaire at what age their child started to walk.

ATTENTION, MOTOR CONTROL, AND PERCEPTION

Deficits in attention, motor control, and perception have been replaced by the initial description minimal brain dysfunction. This may be a sign of impaired neurological development, which is first detectable in preschool children. It has been shown that this condition has a prevalence of 7% among preschool children in Sweden.[14]

We used a questionnaire that was specifically developed to identify children with deficits in attention, motor control, and perception with a reported sensitivity of 74% and a specificity of 92%.[15] One of the original six questions, however, apparently did not identify children with deficits in attention, motor control, and perception in our study. Thus almost one third of parents agreed that their child moved about by "shuffling" before starting to walk implying that as many as one third of the children had signs of deficits in attention, motor control, and perception. When we restricted the analysis to the remaining five questions, 15% of the children in the study were classified as having deficits in attention, motor control, and perception.

POWER CALCULATIONS AND STATISTICAL ANALYSIS

With a given sample size of 1000 children in each group and a two sided α of 0·05 and a β of 0·10, power calculations before the study showed that we would be able to detect a 25% increase in the prevalence of non-right handedness (from a base prevalence of 15-21%). Analogously, a 50% increase in left handedness from a prevalence of 9-13% and a 75% increase in the prevalence of deficits in attention, motor control, and perception from 5-9% would be detected. Power calculation of the hypothesis of impaired neurological development during the first year of life had not been done before the study.

Analyses were done with the statistical package for the social sciences.[16] We compared proportions of missing data between groups with Mantel-Haenszel χ^2 statistics. The associations between routine ultrasonography and subsequent handedness; neurological impairment; and deficits in attention, motor control, and perception were assessed by using the odds ratio as a measure of relative risk. The precision of the odds ratio is presented as 95% confidence intervals, calculated from Mantel-Haenszel χ^2 statistics.[17] Differences in the mean age at walking between the two groups of children was tested with Student's t test. The handedness score was compared between groups with the Mann-Whitney test.

Data were collected from randomised controlled trials in two centres with identical study design and method of randomisation. The analyses were first done stratified by centre but as the results were homogeneous pooled estimates are presented.

Results

Of 1244 children in the screened group, 1115 were studied; five had died (two of congenital heart disease and three of sudden unexpected death in infancy), and the parents of 124 did not respond to the questionnaire. In the control group of 1184 children, one had died (sudden unexpected death in infancy), and the parents of 137 did not respond to the questionnaire, which left 1046 children to be studied. Data from maternal and child health centres were available for 1107 children in the screened group and for 1033 controls. Information on the Denver developmental screening test, however, was available for only 859 screened children and 798 controls. We found no obvious differences between screened and control children on any of the collected family or social variables (table I) nor between the children included in the analysis of handedness and those excluded because of missing data.

TABLE I—*Family and social variables among 1115 children who had been screened by ultrasound in utero and 1046 children who had not as controls. All children aged 8 and 9 years*

	Screened group		Control group	
	No who responded	No (%)	No who responded	No (%)
One or more in the family* with:				
Allergy	1039	528 (51)	960	458 (48)
Left handedness	1052	356 (34)	983	350 (36)
Dyslexia	1109	158 (14)	1038	139 (13)
Years of education (mother):	1097		1027	
6-9		303 (28)		273 (27)
9-12		547 (50)		540 (52)
>12		247 (22)		214 (21)
Years of education (father):	1045		982	
6-9		246 (24)		241 (25)
10-12		431 (41)		395 (40)
>12		368 (35)		346 (35)
Family economy:	1110		1036	
Good		664 (59)		580 (56)
Medium		418 (38)		424 (41)
Poor		28 (3)		32 (3)
Lived with both parents during childhood	1112	978 (88)	1042	914 (88)

*Among first and second order relatives.

TABLE II—*Number of ultrasound examinations in utero for 1115 children allocated to screening group and 1046 children as controls*

No of ultrasound scans	No (%) in screened group	No (%) in control group
0	37 (3)	846 (81)
1	34 (3)	130 (12)
≥2	1044 (94)	70 (7)
1*	1026 (92)	49 (5)

*At 16-22 weeks' gestation.

Complete data on the 10 selected questions from the handedness questionnaire were available for 1663 children (69%). In addition, we had information on which hand the child used the most before starting school and family history of left handedness for 466 of the children with missing data. Among the 239 children in the screened group for whom some data were missing, 34 (14%) were reported to be non-right handed before starting school, whereas 37 (16%) of 227 children in the control group for whom some data were missing were non-right handed. Among these children, 91 (38%) in the screened group reported to have one or more left handers among their first and second order relatives compared with 85 (37%) in the control group. In total, 356 (34%) screened children reported having a family history of left handedness compared with 350 (36%) control children (table I).

Ultrasonographic exposure in utero of screened and control children is shown in table II. The mean number of scans in the screened group was 2·3 (SD 0·9).

Table III shows the numbers of left handed children and children using either hand equally often in screened and control groups for each item in the questionnaire. With the use of the 10 selected questions we classified 162 (19%) of 861 screened children as non-right handed compared with 120 (15%) of 802 controls (odds ratio 1·32; 95% confidence interval 1·02 to 1·71). Of these, 62 (7%) children in the screened group were classified as left handed compared with 44 (5%) control children (1·34; 0·90 to 2·00). The mean handedness score was 8·70 among screened and 8·95 among control children. The median score was 10 in both groups. The distribution of the handedness score was significantly different between screened and control children (p=0·02).

A total of 1654 children could be included in the analyses of impaired neurological development during

TABLE III—*Use of left hand or either hand among 1115 children who had been screened by ultrasound in utero and 1046 children who had not as controls. All children aged 8 and 9 years*

Question	Screened group			Control group			Non-right handedness*	
	No who responded	No (%) who used left hand	No (%) who used either hand	No who responded	No (%) who used left hand	No (%) who used either hand	Odds ratio	95% Confidence interval
Which hand does child use when it:								
1 Draws†	1095	105 (10)	4 (0)	1022	86 (8)	4 (0)	1·14	0·86 to 1·51
2 Writes†	1094	104 (10)	2 (0)	1022	87 (9)	0	1·15	0·86 to 1·54
3 Deals cards from deck†	973	101 (10)	54 (6)	905	84 (9)	24 (3)	1·40	1·07 to 1·83
4 Uses bottle opener†	970	81 (8)	42 (4)	909	70 (8)	18 (2)	1·35	1·02 to 1·80
5 Throws ball†	1054	78 (7)	103 (10)	990	66 (7)	90 (9)	1·11	0·87 to 1·41
6 Uses toothbrush	1075	88 (8)	45 (4)	1009	76 (8)	44 (4)	1·05	0·79 to 1·40
7 Uses eraser†	1066	91 (9)	62 (6)	1009	81 (8)	50 (5)	1·12	0·88 tp 1·43
8 Uses pair of scissors†	1068	84 (8)	15 (1)	1012	65 (6)	18 (2)	1·14	0·85 to 1·54
9 Threads needle	771	127 (16)	38 (5)	727	111 (15)	17 (2)	1·27	0·99 to 1·64
10 Sews with needle	892	76 (9)	15 (2)	843	60 (7)	12 (1)	1·22	0·88 to 1·69
11 Eats with spoon†	1082	95 (9)	23 (2)	1011	76 (8)	24 (2)	1·12	0·84 to 1·50
12 Presses drawing pin	901	67 (7)	120 (13)	856	62 (7)	81 (9)	1·31	1·03 to 1·67
13 Spreads butter	1062	94 (9)	16 (2)	1003	79 (8)	7 (1)	1·23	0·92 to 1·65
14 Twists off lid	954	114 (12)	83 (9)	903	95 (11)	69 (8)	1·17	0·93 to 1·47
15 Eats with fork†	1062	123 (12)	76 (7)	997	105 (11)	59 (6)	1·17	0·93 to 1·47
16 Takes sweets out of box	971	87 (9)	216 (22)	914	77 (8)	165 (18)	1·26	1·03 to 1·54
17 Holds ice cream cone	1021	72 (7)	241 (24)	959	62 (6)	190 (20)	1·24	1·02 to 1·51
18 Cuts with knife†	1040	95 (9)	18 (2)	989	75 (8)	21 (2)	1·13	0·86 to 1·49
19 Throws dart	920	76 (8)	14 (2)	875	57 (7)	15 (2)	1·21	0·87 to 1·68
20 Handles clothes peg	885	72 (8)	81 (9)	818	50 (6)	60 (7)	1·35	1·03 to 1·76
21 Dials telephone number	1039	69 (7)	50 (5)	970	74 (8)	48 (5)	0·90	0·69 to 1·17

*Non-right handedness=use of left hand plus use of either hand. †Questions used for analysis.

the first year of life. According to the short version of the Denver developmental screening test 75 (9%) of 859 children in the screened group and 73 (9%) of 798 children in the control group had impaired neurological development (0·95; 0·68 to 1·33). In all 2128 mothers reported the age when their child started to walk. The mean age for walking was 12 months in both groups.

A total of 2100 children were included in the analyses of deficits in attention, motor control, and perception. Of the 1081 children in the screened group, 147 (14%) were classified as having deficits in attention, motor control, and perception compared to 163 (16%) of 1019 control children (0·83; 0·66 to 1·05).

Allergies, as reported by the mothers, were equally prevalent among the children in the two groups. About a fifth of the children had experienced one or more episodes of allergy which had been treated with prescribed medication.

Discussion

In this randomised controlled follow up we found a possible association between routine ultrasonography in utero and subsequent non-right handedness among children in primary school. No previous study has examined the relation between ultrasound exposure in utero and handedness of the child. The association with non-right handedness was based on information on 10 out of 21 questionnaire items, on which we had data from 1663 children (69%). The study question on handedness was one of six initially specified hypotheses, which indicates that the probability of one or more of them being significant ($p<0·05$) in the predicted direction by chance is about one in seven ($1-0·975^6=0·14$). Thus, the association ($p=0·04$) between ultrasonography and non-right handedness may be due to chance.

Among the children who were classified as non-right handed we found those who were screened with ultrasound to have an increased prevalence of left handedness. This result was not significant, suggesting that the study had insufficient statistical power to resolve the association between ultrasonography and subsequent left handedness in the child.

A strong feature of this study is that a randomised controlled design rules out many of the possible biases that might influence an association between routine ultrasonography and handedness. None the less, the potential for misclassifying children's handedness owing to imprecise measurement may be a threat to the validity of our finding. The 10 questions on which the analysis was based represent various common activities of daily life that received a fairly high response rate. No attempt was made to select items which were likely to distinguish handedness with particularly high sensitivity and specificity. Although our assessment of handedness may be subject to misclassification, it seems unlikely that the bias is differential, depending on ultrasound exposure. We might, however, anticipate a non-differential misclassification, which would ultimately dilute the estimated association (the odds ratio) and give a result which is biased towards the null value of one.[18]

Since the validity of our finding may rest on the classification of handedness we have shown in table IV how the association with ultrasonography may vary depending on which items from the questionnaire have been included in the analysis. Alternative 1 shows that including items such as holding an ice cream cone and dialling a number on the telephone (which is the only item with a question specific odds ratio less than one) instead of items like eating with a spoon or a fork actually strengthens the association with ultrasound (odds ratio 1·41; $p=0·005$). Conversely, applying another combination of 10 items (alternative 2) would weaken the positive association with ultrasound and give a non-significant result. In alternative 3 we used those items to which at least 90% of each sample responded. This yielded 12 of the 21 items. Alternatives 4 and 5 are combinations using 18 or all 21 items. The problem with the two latter alternatives is the loss of power resulting from incomplete response to the items. Overall, however, the results showed a consistently positive association, suggesting that ultrasound

TABLE IV—*Different approaches to analysis of association between ultrasonography and non-right handedness in children who had been screened in utero and those who had not*

Selection of items from handedness questionnaire	Screened group		Control group		Odds ratio	95% Confidence interval	p Value
	No	No (%) who showed non-right handedness	No	No (%) who showed non-right handedness			
10 Selected items	861	162 (19)	802	120 (15)	1·32	1·02 to 1·71	0·04
Alternative 1*	834	199 (24)	781	142 (18)	1·41	1·11 to 1·79	0·005
Alternative 2†	855	138 (16)	808	110 (14)	1·22	0·93 to 1·60	0·15
Alternative 3‡	917	147 (16)	870	110 (13)	1·32	1·01 to 1·72	0·04
Alternative 4§	679	125 (18)	654	92 (14)	1·38	1·03 to 1·85	0·03
Alternative 5‖	617	105 (17)	593	86 (15)	1·21	0·89 to 1·65	0·2

*10 Items (Nos 1-5, 7, 8, 15, 17, 21), right handedness ≥9/10.
†10 Items (Nos 1-8, 13, 18), right handedness ≥9/10.
‡12 Items (Nos 1, 2, 5-8, 11, 13, 15, 17, 18,21), right handedness ≥10/12.
§18 Items (Nos 1-8, 11-15, 17-21), right handedness ≥15/18.
‖21 Items, right handedness ≥17/21.

screened children had a relative risk of non-right handedness of about 1·3.

We found no association between ultrasonography and impaired neurological development, which agrees with the results of other studies.[19,20] Neurological development during the first year of life was assessed from data collected at maternal and child health centres. The precision of the modified version of the Denver developmental screening test has not been formally evaluated, but the study design precludes that assessment of neurological development would be systematically influenced by the children's exposure to ultrasound in utero.

Analogous arguments related to misclassification would apply to the questionnaire, which was designed to measure deficits in attention, motor control, and perception. In this study as many as 15% of the children were classified as having deficits, but there was no statistical difference between the two groups. The observed prevalence was clearly above the assumed base prevalence of 7%.[14] Thus, the instrument may be inaccurate for measuring these deficits. In a study of Swedish preschool children the reported specificity of the questionnaire was 92%, which indicates that the false positive rate may be rather high.[15]

Data in the present study were analysed according to the "intention to treat" principle. Table II shows that 3% of the children who were offered screening were never exposed to ultrasound in utero whereas 7% of the controls were exposed several times. During the perceived critical time window at 16 to 22 weeks of pregnancy 5% of the controls were scanned and 8% of the screening group were not. Thus, the overlap in ultrasound exposure between the randomised groups was probably of little importance in the interpretation of the results.

In addition, we did exploratory analyses of the association between ultrasound exposure (at 16-22 weeks) and handedness regardless of which screening group the child had been in. By doing so the positive association with non-right handedness was strengthened for 12 of the 21 questions in table III, indifferent for five, and weakened for four questions. The estimated odds ratio of non-right handedness increased from 1·32 to 1·34. After adjusting for family predisposition of left handedness the odds ratio was 1·42.

Many fetuses are exposed to ultrasound from additional sources during pregnancy (fetal heart rate detectors and electronic fetal monitoring).[21] In this study such use should have been evenly distributed between screened and control children[8] but may nevertheless represent a background influence, which may weaken the estimated association between ultrasonography and subsequent handedness.

Women who were randomly allocated to routine ultrasonographic screening were typically examined at weeks 19 and 32 of pregnancy. Although a potential biological effect of ultrasound would focus on the developing fetal brain, it does not seem plausible that the low energy levels emitted for diagnostic ultrasound devices (such as the ADR scanners) would cause damage to the fetal brain. Nevertheless, potential harm caused by cavitational effects in the cells cannot be excluded.[22] Experimental studies in vitro have suggested that ultrasound may influence cell membranes.[3,4] Others have hypothesised that ultrasound exposure in utero may influence neuronal migration during a critical stage,[2] which may influence brain development and be an underlying explanation for changes in handedness patterns, dyslexia, or impaired neurological development. We have previously examined the relation between ultrasonography and dyslexia and found no evidence to support the hypothesis.[8] Thus, the finding of a link between ultrasound and laterality might seem odd, but it is often not recognised just how tenuous the association between dyslexia and lateralisation is.[23]

Clinical implications

- Most women in developed countries have ultrasound examinations during pregnancy
- No problems from the use of ultrasonography have so far been detected
- This study shows a positive association between ultrasound scanning during pregnancy and the proportion of children who are not right handed at the age of 8 and 9 years
- This may be due to chance or it may be the result of ultrasonography's effect on the development of the fetal brain
- This study found no association between ultrasonography during pregnancy and impaired neurological development of the child

The present study does not indicate any association between ultrasound in utero and impaired neurological development. We are, however, left with an unexplained positive association between ultrasound screening and non-right handedness. This is one possible chance finding among a number of non-significant findings. Theoretically, the concept of pathological left handedness[6] implies that children with early brain damage to the left hemisphere will have an increased incidence of left handedness. A left hemisphere lesion, however subtle, may cause a shift in hand preference in otherwise genotypic right handers, thus increasing the overall percentage of non-right handedness in these children.[6] Increased incidence of non-right handedness in a particular population may therefore be a sensitive index of subtle changes in the development of the brain or parts of the brain. We would, however, emphasise the need to replicate the positive association between ultrasound and non-right handedness before it is interpreted as more than a chance finding. Follow up of the children from the Swedish,[24] Finnish,[25] or other randomised controlled trials of ultrasonography in pregnancy may help clarify this issue.

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Case-control study of congenital anomalies in children of cancer patients

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Abstract

***Objectives*—To determine whether the offspring of cancer survivors are at an increased risk of congenital anomalies and whether cancer therapy before conception is associated with such an increase.**

***Design*—Case-control study using computerised record linkage.**

***Setting*—Ontario, Canada.**

***Subjects*—Parents of children born during April 1979 to December 1986 who had a congenital anomaly diagnosed within the first year of life (45 200 mothers and 41 158 fathers) and a matched sample of parents whose children did not have a congenital anomaly (45 200 mothers and 41 158 fathers).**

***Main outcome measures*—Cancer diagnosed in either parent before conception and radiotherapy to the pelvis or abdomen or chemotherapy with an alkylating agent.**

***Results*—Among the mothers, 54 cases and 52 controls were identified as having had cancer diagnosed in Ontario (relative risk=1·04, 95% confidence interval 0·7 to 1·5) and among the fathers, 61 cases and 65 controls were identified (0·9, 0·7 to 1·4). No significant associations were found between congenital anomalies in the offspring and any type of cancer treatment in either the mothers or the fathers.**

***Conclusions*—The risk of congenital anomalies among liveborn offspring whose parents have had cancer or been treated for cancer is not higher than that in the general population.**

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Introduction

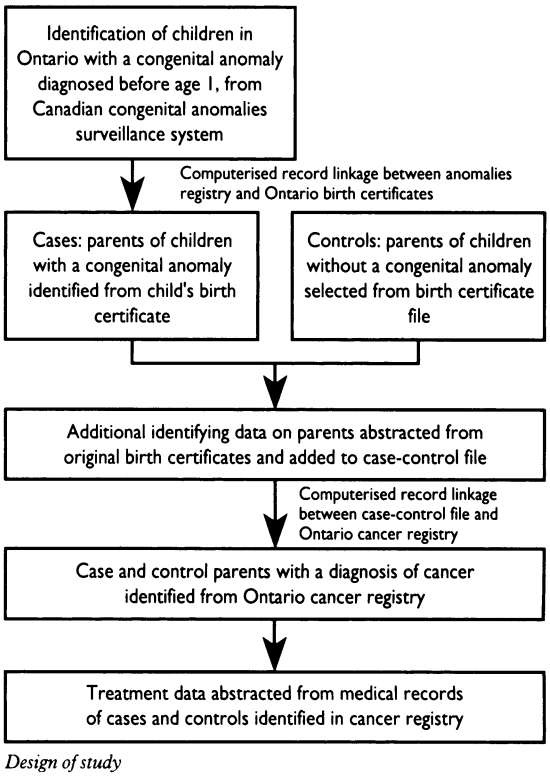
The survival rate for children and young adults with cancer have improved substantially over the past few decades[1,2] largely because of advances in treatment. In the 1970s, chemotherapeutic drugs used in combination were shown to increase complete remission rates. Thus, many children or young adults treated for cancer in the past 10-15 years will have received multiple chemotherapeutic drugs, possibly in addition to radiotherapy.[3] Because much of the treatment is known to be mutagenic and is designed to interfere with the DNA and normal cellular function, there may be adverse effects on reproduction.

Although some animal studies support the relation between radiation and chemical exposure and abnormalities in the offspring,[4-6] evidence in humans is inconclusive. The higher rates of adverse reproductive outcomes, including congenital anomalies, found among mothers treated with radiotherapy before conception are thought to be primarily due to radiation induced uterine damage rather than to germ cell mutations.[7-9] Although most studies have not found an association between cancer therapy and congenital anomalies in the offspring,[7,10,11] the power to detect moderate increases in risks has generally been limited and few have looked specifically at conditions that might be expected to result from a therapy induced germ cell mutation.

We conducted a case-control study to determine the association between congenital anomalies in the children of those who had cancer diagnosed or treated before conception. We also examined the risks associated with specific cancer therapies and the risks of specific anomalies that could be produced by a new mutation.

Subjects and methods

The figure summarises the methods used in the study. Cases were defined as the parents of children who were recorded in the database of the Canadian



Design of study